

Comparison of the Effect of Botulinum Toxin Injection Under Ultrasound Guidance and Oral Propranolol in the Treatment of Moderate to Severe Essential Hand Tremor

Bahador Asadi¹, Sara Hassani^{2*}, Hossein Ghanaati³, Aryobarzan Rahmatian⁴, Mobin Azami⁵, Saeed Amiri Gheshlaghi⁶

- 1- Department of Neurology, AJA University of Medical Sciences, Tehran, Iran
- 2- Pennsylvania Diagnostic Radiologist post-doctoral research fellowship, university Perelman school of medicine, Philadelphia, USA
- 3- Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Science, Tehran, Iran
- 4- Department of Radiology, Tehran university of Medical Science, Tehran, Iran
- 5- Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran
- 6- AJA University of Medical Sciences, Tehran, Iran

Abstract

Background: Tremor is one of the most common movement disorders affecting the upper limb (proximal and distal), neck, or vocal cords. Primidone and propranolol are the most effective oral medications prescribed for essential tremors. 12 to 66% of those treated with propranolol have complications, and 30% of patients do not respond to oral medications.

Methods: In this study, a clinical trial was conducted to compare the effect of botulinum toxin Injection and Oral Propranolol in the Treatment of essential hand Tremor on patients referred to Golestan Hospital's neurology clinic complaining of hand tremor in 2016 and 2017. Eighty essential tremor patients were assigned to the study and divided into two groups, the botulinum toxin group had muscular injection under ultrasound guidance, and the propranolol group received oral propranolol. Patients were evaluated at one-month intervals, weeks 0, 4, 8, and 12. The severity of the tremor was assessed using the TETRAS clinical scale. Another patient evaluation was the RAND SF-36 Quality of Life Questionnaire, which was presented to patients at weeks 0 and 8.

Results: Our findings in this study revealed that the intramuscular injection of botulinum toxin is more effective in treating moderate-to-severe Essential Tremor hand than the intake of oral propranolol.

Conclusion: Botulinum toxin is recommended for moderate-to-severe cases of essential hand Tremor, especially for patients who fail to bear the treatment course or take several medications that prompt striking drug interference.

Keywords: Essential Tremor, Botulinum toxin, propranolol, Ultrasound

*Correspondence to Sara Hassani, Philadelphia Pennsylvania Diagnostic Radiologist post-doctoral research fellowship, university Perelman school of medicine, Philadelphia, USA

Email:
sara.hassani@pennmedicine.
upenn.edu

Published online 30 July
2023



Cite this article as: Asadi, B., Hassani, S., Ghanaati, H., Rahmatian, A., Azami, M., Amiri Gheshlaghi, S. Comparison of the Effect of Botulinum Toxin Injection Under Ultrasound Guidance and Oral Propranolol in the Treatment of Moderate to Severe Essential Hand Tremor. *Neurology Letters*, 2023; 2(2): 69-77. doi: 10.61186/nl.2.2.69

Introduction

Tremor is one of the most common movement disorders, defined as rhythmic involuntary movements. It is caused by intermittent or simultaneous irregular contractions of muscles that have a reciprocal effect. Having oscillating nature distinguishes it from Myoclonus and Asterixis(1). Essential or

familiar tremor is the most common type of tremor characterized by a state of kinetic and postural tremor with a frequency of 4 to 8 Hz. It is not associated with other neurological disorders. Essential tremor affects the upper limb (proximal and distal), neck, or vocal cords. Anxiety, alcohol craving, exercise, fatigue, and drugs such as lithium and beta-adrenergic exacerbate this disease (2). Alcohol consumption

in 50-90% of patients reduces the amount of tremor, but the tremor is temporarily worse after the disappearance of the alcohol effect (3).

Primidone and propranolol are the most effective oral medications prescribed for the treatment of essential tremor. Primidone is an anti-convulsive drug, and propranolol is a non-specific antagonist of beta-adrenergic receptors. Propranolol is the only drug approved by the Food and Drug Administration (FDA) for this purpose (4). These drugs have several complications, including dizziness, fatigue, orthostatic hypotension, and bradycardia (5). These complications happen in 12 to 66% of those treated with propranolol (6).

Moreover, 30% of patients do not respond to oral medications, which most patients cannot use (7). One of the invasive therapies available for patients resistant to treatment is thalamotomy surgery or deep brain stimulation in the thalamus using electrode implanting. This therapy may be effective but can be performed on patients under 75. In addition, the device settings are unclear and obscure after the surgery (8, 9).

Oral medications have been used more than other mentioned treatments. However, elderly patients' treatment is challenging because they take several medications due to other chronic diseases, which cause drug interactions or intolerance to side effects. Especially, propranolol causes complications such as orthostatic hypotension, dizziness, and bradycardia that aggravate in elderly or diabetic patients (10). Therefore, finding non-edible treatment methods has always been a concern for researchers. Another non-edible method is an intramuscular injection of botulinum toxin type A, which has been considered an effective treatment for dystonia, spasticity, and other motor disorders. Recently, various studies have shown that it can help treat essential tremors (11-14).

Currently, there are contradictory results which might be due to the different techniques and methods among studies. All studies done to treat essential tremors by botulinum toxin injection have been conducted to compare the effect of this method with a placebo. Only a study evaluated botulinum toxin injection in treating crucial vocal tremor with oral propranolol (4); however, they haven't been compared. The present clinical trial aimed to consider the radical differences in the effect of botulinum toxin injection with oral treatment in the case of essential hand tremor.

Methods

Participants

This study protocol was approved by the AJA University of Medical Sciences Ethics Committee (IRCT201607022415N2). This study was a single-center, single-injector, single-blind randomized clinical trial. The statistical population included patients referred to Golestan Hospital's neurology clinic complaining of hand tremor in 2016 and 2017. Ninety-two patients were randomly assigned to the study by a neurologist after confirming the diagnosis of essential tremor; of these, only 80 had included the criteria for the study. Samples included in this study had a postural tremor severity equal to or greater than two, according to section 4 of the TETRAS v3.1

clinical scale. They also had normal thyroid function tests. In this study, patients taking tremor-inducing drugs (such as lithium, valproate, salbutamol, etc.), pregnant women, and cow's milk protein-sensitive individuals (contraindication for botulinum toxin injections) were excluded. In addition, People with contraindications for administration of propranolol, such as conductive Heart disease, congestive heart failure, diabetes, asthma, etc., those who have had a history of botulinum toxin injections in the upper limb, those who had a history of botulinum toxin injections in the last eight months at any point of the body, those who were botulinum toxin-sensitive, myasthenia gravid or myasthenia suspect, those with Parkinson disease, and also people taking anti-dopaminergic drugs were excluded.

Finally, 80 patients with the required criteria were identified and imported into the study after providing the necessary explanations and consent. Then, they were randomly divided into two groups, botulinum toxin or propranolol, using a simple randomization technique. The botulinum group (31 patients) had muscle injections, and the propranolol group (49 patients) received oral propranolol.

If patients were taking medications for tremors, their drugs were discontinued for one week before the intervention to prevent interference. Patients were evaluated at intervals of one month at weeks 0, 4, 8, and 12. The severity of postural tremors was assessed using the tremor research group essential tremor rating assessment scale (TETRAS) (Section 4) in all visits. In this method, the patient holds both hands in full extension and parallel with the ground for 5 seconds while the fingers are in abduction. The examiner evaluates the tremor domain at the point of the hand with the most significant displacement and allocates the correct score. This rating can be one of the numbers 0, 1, 1.5, 2, 2.5, 3, 3.5, or 4. It should be noted that the same examiner evaluated all patients and was unaware of the type of intervention performed for them.

Quality of life assessments

Another patient evaluation was the RAND SF-36 Quality of Life Questionnaire, which was presented to patients at weeks 0 and 8. The questionnaire has 36 multiple-choice questions, and a score is allocated to each question according to the individual's response in which different scales are examined, including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. Illiterate patients filled out the questionnaire with the help of the examiner. The questionnaire measured the patient's blood pressure and pulse rate each visit. In the end, 14 patients refused to continue the study at different stages. Only 80, 75, and 66 patients in this study visited the fourth, eighth, and twelfth weeks, respectively.

Intervention

The injected botulinum toxin type A in Botulinum group patients was Dysport® (abobotulinumtoxinA), produced by IPSEN. This injection was performed intramuscularly in the

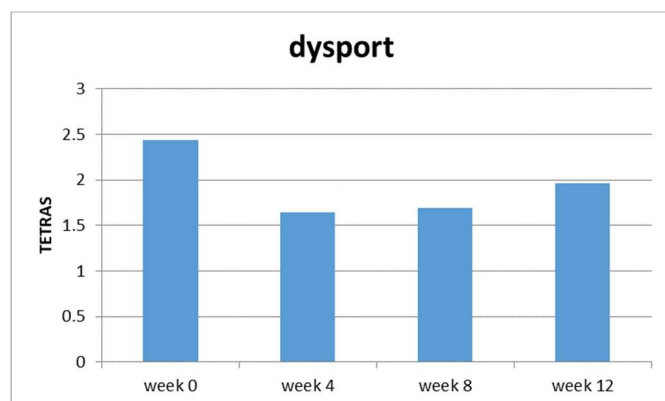
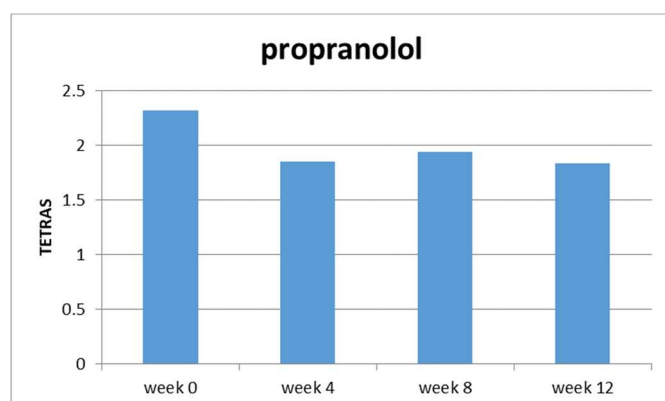


Figure 1. The severity of tremor in the Dysport group at weeks 0, 4, 8, and 12



flexor carpi radialis (25-50 units), flexor carpi ulnaris (25-50

Figure 2. The severity of tremor in the propranolol group at weeks 0, 4, 8, and 12

units), and pronator teres (75-50 units). A sonography guide was used to select the muscles and determine the dose. The selection of injected muscle was based on the direction of the tremor (flexion-extension or supination-pronation or both) and the neurologist's decision. The dose of Dysport was determined by the neurologist based on the muscle volume and the tremor's severity. One ml of normal saline was used for injection for 100 units of Dysport, and a 30-gauge needle was used for injection.

The dose of propranolol was determined based on the severity of the tremor and according to patient tolerance and complications between 60 and 120 mg/day (in divided doses). In this study, propranolol tablets were manufactured by Abidi® Pharmaceutical Company. During each visit, the patients were questioned and reported the complications of Dysport injections, including muscle weakness, hematoma, injection site pain, and allergic reaction.

Statistical analysis

The data were analyzed using IBM® SPSS® version 21. The ANOVA test was employed to analyze the differences between the mean values of the variables studied across the two groups. A P value less than 0.05 was considered significant.

Results

Statistical analysis shows no significant difference between the two groups regarding the basic values of variables. A total of 80 patients with essential hand tremor participated in this study. Of these, 31 patients were randomly assigned to the Dysport group, and 49 subjects in the propranolol group. The mean age of the subjects was 69.06 years old. Forty-four subjects (55%) were men, and 36 subjects (45%) were women (Table 1).

The average dose of injected Dysport is 125.88 for each hand and 251.77 per person. Oral propranolol was prescribed with an average maximum dose of 80.41mg daily. In the follow-up process, we collected data related to 80 people during the first month (week 4), 75 in the second-month visit (week 8), and 66 in the third-month visit (week 12).

During all visits, the tremor severity was evaluated according to TETRAS Tremor Clinical Scale, and the score was recorded. Based on the repeated measure ANOVA test, there was a significant difference in the severity of tremors among time points in the Dysport group. Mauchly's hypothesis was accepted in this test due to the lack of significance in the trial ($F = 108.27$; $p < 0.001$). Tremor severity decreased significantly in week 4 (1.64 ± 0.41) and week 8 (1.69 ± 0.41) compared to the baseline value (2.44 ± 0.37) ($p < 0.001$). Despite the increased severity of tremors in week 12 (1.96 ± 0.39), there is also a significant decrease compared to the baseline value ($p < 0.001$).

In addition, the results showed that tremor severity was not significantly different in the 8th week compared to the 4th week ($p > 0.05$). However, at week 12, the tremor severity was significantly higher than in week 8 ($p < 0.001$). As shown in the graph, the highest reduction in tremor severity was observed in the Dysport group at week 4. These comparisons have been

Table 1. Demographic characteristics of participants in this study

Variable	(Percent) number
Average age	69.06
Gender	
Male	(55%) 44
Female	(45%) 36
Type of intervention	
Dysport	31
Average age	71.61
Gender	
Male	17(54.8%)
Female	14(45.2%)
Propranolol	49
Average age	67.45
Gender	
Male	27(55.1%)
Female	22(44.9%)
Average Dysport unit	
Per each limb	125.88
Per person	251.77
Maximum average propranolol dose (mg)	80.41

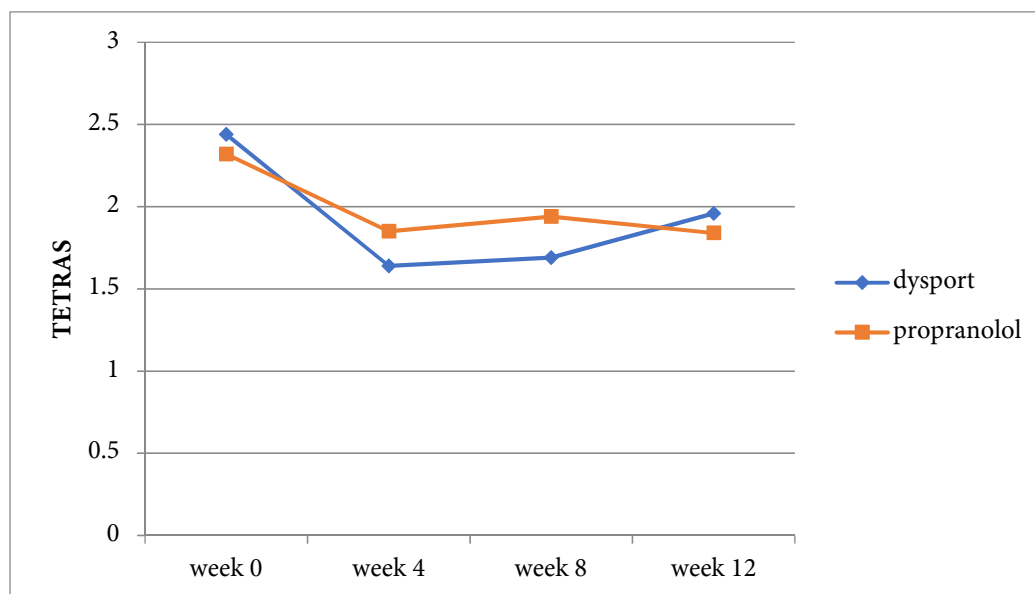


Figure 3. Comparison of recovery rates in different groups

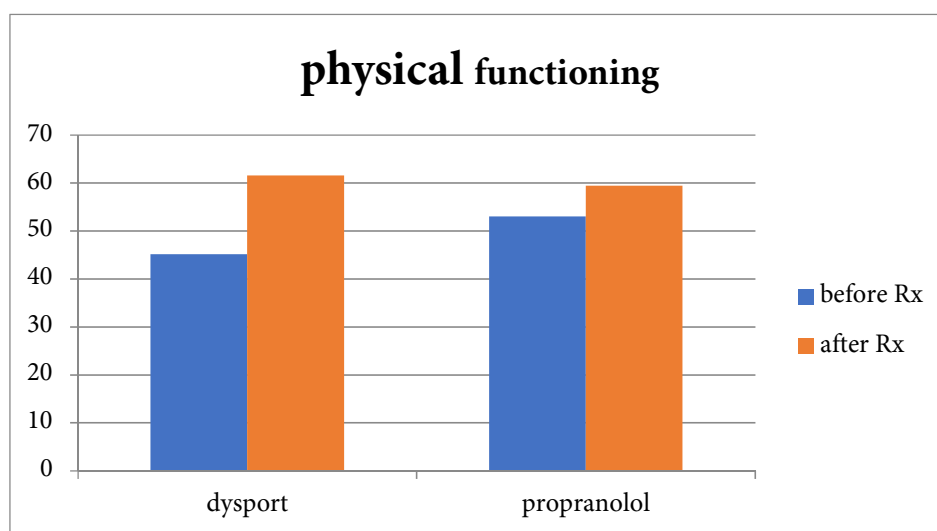


Figure 4. Comparison of recovery rates in different groups

made with Bonferroni correction. There was also a significant tremor severity difference amongst time points in the propranolol group using the repeated measure ANOVA test ($p < 0.001$).

The severity of tremors was significantly decreased in week 4 (1.85 ± 0.44), week 8 (1.94 ± 0.47), and week 12 (1.84 ± 0.42) compared to the base value (2.32 ± 0.33) ($p < 0.001$). It should be noted that the severity of tremors increased significantly ($p = 0.036$) in week eight compared to week four and decreased considerably in week 12 compared to week 8 ($p = 0.013$).

The tremor severity improvement in the Dysport group was more significant than propranolol at week 4, according to linear regression analysis. This significant excellence of Dysport is also seen in week 8. Data analysis does not show a significant difference between the two groups at week 12 (table2 and Figure 3).

Quality of life questionnaire analysis showed that the physical functioning subscale increased significantly in week 8 (61.55 ± 21.55) compared to the pre-intervention on botulinum toxin (45.17 ± 22.13) ($t = -10.07$; $df = 28$; $p < 0.001$). This subscale increased significantly in the propranolol group at week 8

(59.15 ± 20.11) compared to pre-treatment as well (53.4 ± 18.45) ($t = -5.38$; $df = 45$; $p < 0.001$). Linear regression was used to compare the effect of two treatments on pre-treatment. The results showed that the improvement of this subscale in the Dysport group with a mean improvement of (16.37 ± 8.75) was higher than the propranolol group with a mean improvement of (6.41 ± 8.07) ($\beta = -0.22$; $p < 0.001$) (Table 3 and Figure 4).

The other factor considered in this study was role limitations due to physical health, to which the paired sample t-test was applied. The Dysport group showed a significant increase of this indicator revealed at week 8 (67.24 ± 29.20) than pre-treatment (33.62 ± 28.56) ($t = -7.43$; $df = 28$; $p < 0.001$). In addition, the propranolol group showed that there was a significant increase in this group at week 8 (54.89 ± 28.19) compared to week 0 (44.46 ± 27.34) ($t = -3.60$; $df = 45$; $p = 0.001$). We compared the improvement of this indicator between the two groups using linear regression. The results showed that the improvement of this indicator in the Dysport group, with a mean improvement of (33.36 ± 24.34), was higher than in the propranolol group, with a mean

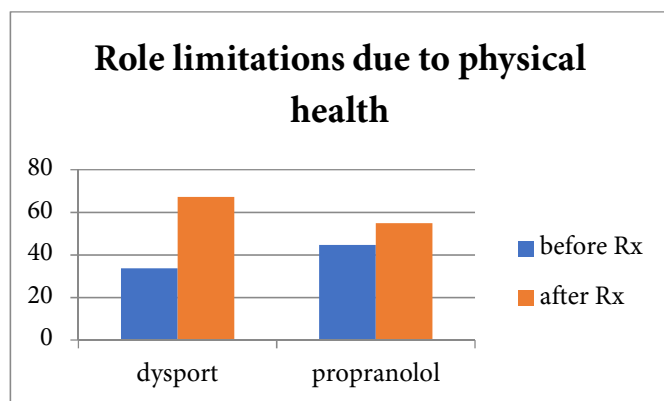


Figure 5. Comparison of recovery rates in different groups

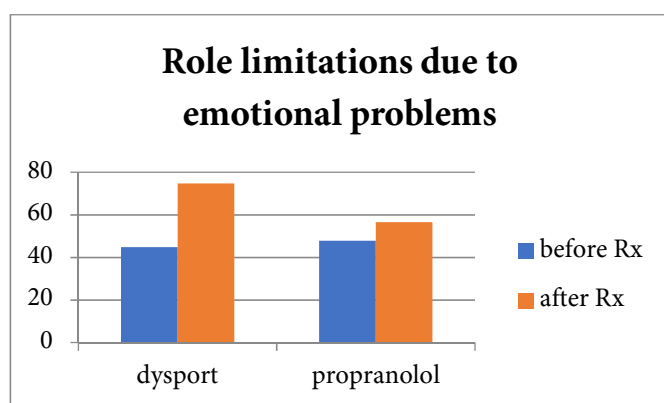


Figure 6. Comparison of recovery rates in different groups

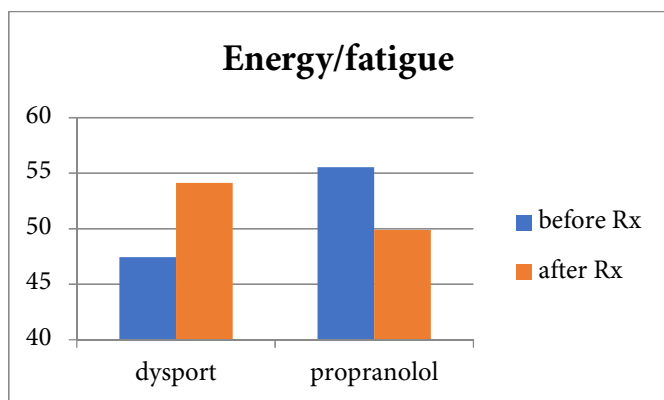


Figure 7. Comparison of recovery rates in different groups

improvement of (19.41 ± 10.32) ($\beta = -0.34$; $p < 0.001$) (Table 3, Figure 5).

The role limitations due to emotional problems were evaluated using the paired sample t-test. The pre-treatment mean in the Dysport group was 44.78 ± 27.11 , which increased in week 8 to 29.09 ± 74.68 . The paired sample t-test showed that this increase was significant ($t = -5.61$; $df = 28$; $p < 0.001$). In the propranolol group, the mean indicator increased from 47.78 ± 29.51 before treatment to 56.49 ± 35.04 . This increase was significant ($t = -2.60$; $df = 45$; $p = 0.01$). A comparison of the two groups showed that the Dysport group's improvement

(29.89 ± 28.65) was significantly higher than the propranolol group (22.70 ± 8.70). ($B = -0.29$; $p = 0.001$) (Table 3, Figure 6). The results of the energy/fatigue subscale for the Dysport group showed a significant increase at week 8 (21.21 ± 54.13) compared to pre-treatment (47.24 ± 22.02) ($t = -3.08$; $df = 28$; $p = 0.005$). This indicator in the propranolol group decreased from 55.54 ± 21.50 before treatment to 49.89 ± 22.52 in week 8. This decrease was statistically significant ($t = 4.63$; $df = 45$; $p < 0.001$). The comparison between the two groups with linear regression showed that the two groups have a significant difference in terms of this indicator, although their variations were different ($\beta = -0.26$; $p < 0.001$) (Table 3, Figure 7).

The results of the paired sample t-test for the study of emotional well-being in the Dysport group indicated that the indicator increased significantly in week 8 (54.20 ± 20.69) compared to week zero (48.41 ± 22.83) ($t = -4.14$; $df = 28$; $p < 0.001$). In the propranolol group, the indicator showed a significant increase after treatment (55.04 ± 24.50) compared to pre-treatment (51.65 ± 24.69) ($t = -4.36$; $df = 45$; $p < 0.001$). Although the Dysport group (7.52 ± 5.79) had a mean improvement over the propranolol group (3.36 ± 5.26), linear regression showed no significant difference between the two groups ($\beta = -0.04$; $p = 0.13$) (Table 3, Figure 8).

The evaluation of the social functioning indicator showed a significant increase in this index at week 8 (60.94 ± 21.92) compared to pre-treatment (52.15 ± 20.61) ($t = -2.79$; $df = 28$; $p = 0.009$). The same analysis in the propranolol group showed that this indicator significantly increased in week 8 (58.36 ± 23.37) compared to pre-treatment (52.21 ± 23.26). Linear regression revealed that there was no significant difference between the two groups ($\beta = -0.04$; $p = 0.56$), although there was a greater improvement in the Dysport group (8.17 ± 15.76) than propranolol group (6.22 ± 12.28) (Table 3, Figure 9).

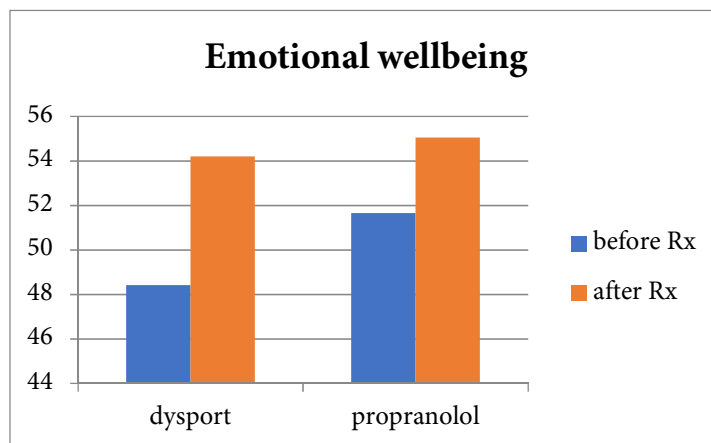
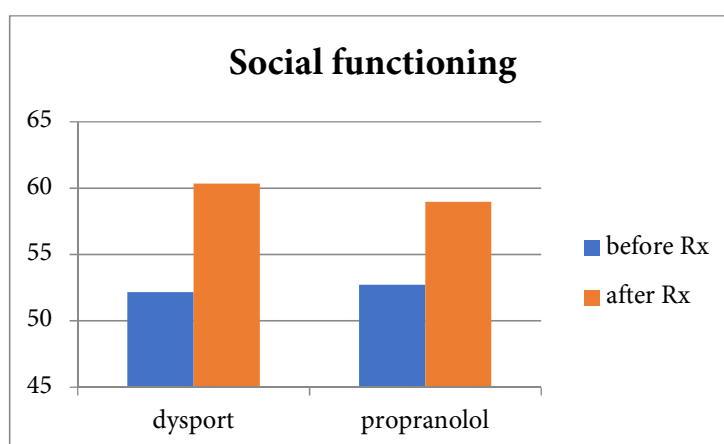
The pain subscale analysis showed no significant difference between the values before and after treatment in the Dysport group ($t = -1.85$; $df = 28$; $p = 0.07$). There was also no significant difference between the pre-treatment (61.57 ± 21.40) and after-treatment (61.08 ± 22.05) in the propranolol group, but even though the values were not significant before and after treatment, the two groups showed a significant difference ($\beta = -0.10$; $p = 0.039$) based on linear regression analysis (Table 3, Figure 10).

The results showed that in the Dysport group, the general health subscale had a significant increase after the treatment (19.77 ± 64.13) in post-treatment compared to the baseline values (51.30 ± 19.30) ($t = -7.99$; $d = 28$; $p < 0.001$). In the propranolol group, there was a significant increase in post-treatment levels (59.67 ± 20.88) compared to baseline (54.47 ± 19.49) ($t = -42.2$; $df = 45$; $p < 0.001$). The improvement rate of this indicator in the Dysport group (12.93 ± 8.71) was significantly higher than the propranolol group (7.85 ± 4.89) ($\beta = -0.19$; $p < 0.001$) (Table 3, Figure 11).

It is also worth noting that from 31 patients who were injected with Dysport, three subjects (9.67%) reported mild and transient finger weakness. And two subjects (6.45%) reported pain at the injection site. No case of allergic reaction to botulinum toxin was reported.

Table 2. Representation of the recovery rate of Dysport and propranolol in weeks 4, 8, and 12 in the Dysport and propranolol groups.

Time	The average difference compared to the baseline		β (confidence interval 95%)	P-value
	Dysport	Propranolol		
Week 4	0.8-	0.47-	-0.2	0.001>
Week 8	0.75-	38-	-0.21	0.001>
Week 12	48-	48-	(-0.12)	0.005>

**Figure 8.** Comparison of recovery rates in different groups**Figure 9.** Comparison of recovery rates in different groups

Discussion

Essential tremor is one of the most common movement disorders that are directly age-related, is mainly witnessed in family members, and is also an inherited factor. In severe cases, it can disrupt the everyday and occupational activities of the individual and even psychologically causes depression. From the social point of view, it imposes a relatively heavy economic burden, and its psychosocial consequences can be vast. Mainly, in societies facing the aging process, this will be more likely to be experienced because the person will not be able to do their personal affairs and will depend on the help of others with the severity of the illness (15).

Various treatments have been presented so far for this disease, but some do not affect a part of the patients. Sometimes unwanted and unpleasant side effects make many people get discontinue. This issue is becoming more important because most patients are older adults taking many medications for

other reasons (16). Drug interactions and the difficulty of consuming multiple doses make the problem even more complex. Some other therapies, such as electrode placement in the brain, are invasive and can only be used in specific cases. They require experienced physicians and advanced medical facilities, which are highly prohibitive and risky due to their invasive nature. In the past, botulinum injection had been used to treat other disorders, such as spasticity and dystonia, and proved successful and effective. The studies conducted also confirm the effectiveness of this method in the treatment of tremors (17).

In this study, we compared two treatment methods for essential tremor, i.e., oral propranolol and botulinum toxin type A intramuscular injection, which have not been done so far. The obtained results showed that Dysport injections significantly reduced the severity of the hand tremor at weeks 4 and 8, more significantly than propranolol ($p < 0.001$). The peak effect of Dysport in this study was obtained at week 4,

which is consistent with the results of previous studies that indicate the maximum impact of Dysport occurs at weeks 4 to 8 (16). After four weeks, a significant increase was observed in the tremor severity up to week 12, but it is still significantly lower than the baseline value ($p < 0.001$). This pattern is consistent with a study by Samotus et al. (2016) (17). The reason for this pattern is that the clinical effect of botulinum toxin injection is reduced after 12 to 14 weeks from injection due to neuronal sprouting at the site of chemical neurolysis. In previous studies of botulinum toxin, it has been shown that injection should be repeated after three months, and a slow cumulative effect is observed after repeated infusion. Then the interval between injections can be increased (18).

Regarding the quality of life, the result of this study demonstrates that the physical functioning indexes, role limitations due to physical health and emotional problems, as well as energy/fatigue, and general health improved significantly by the injection of Dysport compared to the propranolol ($p \leq 0.001$). Considering that one of the side effects of propranolol is fatigue and lethargy, the result seems justifiable.

There were no significant differences between the two therapeutic methods in improving the indicators of emotional well-being and social functioning ($p > 0.05$). This was also true about pain in both groups before and after the treatment. It seems that both treatments failed to play an influential role in alleviating the physical pain, but in other indexes, they prompt better post-treatment conditions. (Except for energy/ fatigue in the propranolol group and physical pain in both groups) Previous studies that have been published so far have reported some contradictory results. Trosch et al. concluded that botulinum toxin injection does not dramatically reduce the tremor's amplitude but improves subjective symptoms. This

appears to be due to the botulinum toxin blind injection that caused the muscles responsible for the tremor not to be appropriately injected (19). Jankovic et al. observed significant improvement in tremor severity but did not substantially improve the functional scale (20). According to the study, injections were also blind but two-stage, and almost all patients reported some degree of weakness in their fingers. The use of fixed doses for all patients and the lack of a guide for injections are fundamental causes that do not result in functional improvement in patients. Brin et al.'s study showed a significant reduction in the severity of tremors, but functional disability was not significantly improved (11). Again, this study used fixed doses for all patients, and an EMG guide was used for injection. However, in Pacchetti et al., which also used electromyography for injection, there has been a significant improvement in severity and function (21). In the Samotus et al. study, the same pattern as our study was obtained, and the kinematic evaluations were used to determine the dose and injections with a guide of electromyography (14).

It seems that if the botulinum toxin is injected with the appropriate guide and an individualized dose is selected for each patient, depending on the severity and type of tremor, it can increase the rate of improvement after treatment. In our study, ultrasonography was used for injection, rapidly expanding. This method is inexpensive, available, and non-invasive, and the physician can see the injected muscle directly; it reduces the effects of muscle weakness on the fingers and, on the other hand, improves outcomes. Complications were less than in similar studies (12, 15, 16), and only 9.67% (3 patients) had muscle weakness. As mentioned, one of the reasons is ultrasound guide use. In

Table 3. Comparison of different variables between two groups

Subscale	Group	Pre-treatment	Week 8	Average difference	β	p-value
Physical functioning	Dysport	45.17	61.77	16.37	0.22-	0.001>*
	Propranolol	53.04	59.44	6.41		
Role limitations due to physical health	Dysport	33.62	67.24	33.62	0.34-	0.001>*
	Propranolol	44.56	54.89	10.32		
Role limitations due to emotional problems	Dysport	44.78	74.68	29.89	0.29-	0.001>*
	Propranolol	47.78	56.49	8.7		
Energy/fatigue	Dysport	47.24	54.13	6.89	0.26-	0.001>*
	Propranolol	55.54	49.89	5.65-		
Emotional well-being	Dysport	48.41	54.2	5.79	-0.04	0.13
	Propranolol	51.56	5	3.39		
Social functioning	Dysport	52.15	60.34	8.18	-0.04	0.56
	Propranolol	52.71	58.96	6.25		
Pain	Dysport	54.74	59.05	4.31	-0.1	0.039*
	Propranolol	61.57	61.07	-0.49		
general health	Dysport	51.2	64.13	12.93	-0.19	0.001>*
	Propranolol	54.78	59.67	4.89		

* significantly different between groups

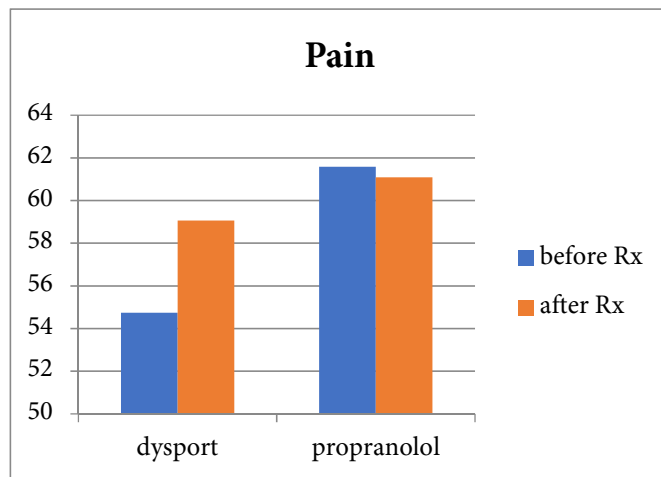


Figure 10. Pain subscale analysis between the values before and after treatment in the Dysport group

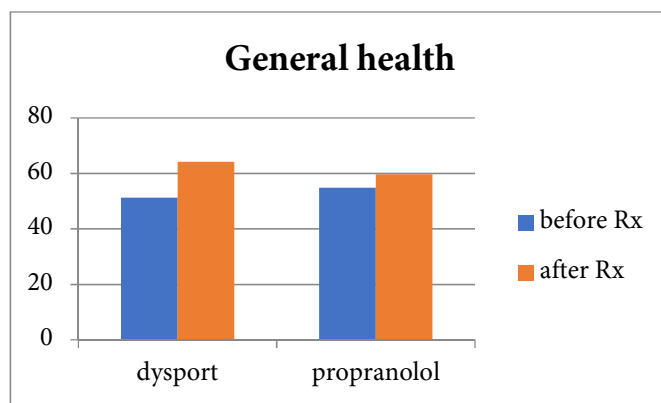


Figure 11. Results of the comparison between the Dysport group general health subscale showed a difference after the treatment.

addition, the experience and skill of the injecting physician are also essential.

Another case in which the results can be noticed is the fluctuation of tremor severity in the propranolol group. The seriousness of tremors in this group first fell in week 4, then increased in week 8, and fell again in week 12. Since the half-life of propranolol is short, regular use of it throughout the day is essential. However, we tried to make assessments steadily throughout the day, and one of the reasons may be the same. On the other hand, the dose of propranolol has been determined according to the patient's tolerance and complications, which may have been reduced during a visit because of side effects, or the dose may increase to improve the healing in case of patient bearing, which can be the reason of this pattern in the results.

Considering that there has not been any study on the comparison of oral treatment with botulinum toxin injection in the treatment of essential hand tremor, the results of this study showed that botulinum toxin injection induced a more significant improvement in the severity of essential hand tremor in moderate to severe cases in weeks 4 and 8 compared

with oral propranolol administration. In addition, patients' quality of life (except in the index of social functioning and emotional well-being) is increased compared with propranolol, but its effect decreases at week 12. Therefore, it is recommended to use repeated botulinum doses at appropriate intervals. These results indicate that in medium to severe cases of essential hand tremor, botulinum toxin injection can be reliably used, especially in those who do not tolerate or are resistant to oral treatments or those who are suffering from other diseases simultaneously and taking several medications and are reluctant to take more medications.

One of the limitations of this study is the blindness of patients, which is very difficult due to the different nature of the two treatments (oral and injectable); it may affect the questionnaire results, although the person evaluating the severity of the tremor was not aware of the type of treatment. Moreover, evaluations will be more accurate if more modern methods, such as kinematics, are used in assessments. For further studies, it is recommended to compare oral medication and Botulinum injections in treating essential tremors using repeated injection courses for more extended periods. Other drugs, such as primidone, can also be used for comparison. In addition, comparing different methods of botulinum toxin injection, such as comparing injection with an ultrasonography guide vs. an electromyography guide, can be valuable.

Conclusion

Our findings in this study revealed that the intramuscular injection of botulinum is more effective in treating moderate-to-severe Essential Tremor hand than the intake of oral propranolol. According to our findings, the severity of hand tremors and most of the quality of life indexes improve more with the injection of botulinum compared to the oral intake of propranolol. Based on the results, the injection of botulinum toxin is recommended for moderate-to-severe cases of essential hand tremor, especially for patients who fail to bear the treatment course or take several medications that prompt striking drug interference.

Declarations

Funding

The authors received no financial support for the research.

Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Code availability

Not applicable

Authors' contributions

SH, BA, MA and AR analyzed and interpreted the patient data. AB, MA and SAG were the major contributors in writing the manuscript. SH designed and conceptualized the study and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Ethical approval

Clinical Research Ethics Committee of AJA University of Medical Sciences (IRCT201607022415N2) approved the study (Ethics code: IR.AJAUMS.REC.1400.230). All the methods were performed in accordance with the Ethics Review Board. All the patients read and signed informed consent.

Consent for publication

This manuscript has been approved for publication by all authors.

References

- Ellenbogen RG, Abdulrauf SI, Sekhar LN. Principles of Neurological Surgery E-Book: Expert Consult-Online: Elsevier Health Sciences; 2012.
- Lou J-S, Jankovic J. Essential tremor Clinical correlates in 350 patients. *Neurology*. 1991;41(2 Part 1):234-.
- Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. *Annals of neurology*. 1994;35(6):717-23.
- Justicz N, Hapner ER, Josephs JS, Boone BC, Jinnah HA, Johns MM. Comparative effectiveness of propranolol and botulinum for the treatment of essential voice tremor. *The Laryngoscope*. 2016;126(1):113-7.
- Rajput AH, Rajput A. Medical treatment of essential tremor. *Journal of central nervous system disease*. 2014;6:29.
- Zesiewicz T, Elble R, Louis E, Hauser R, Sullivan K, Dewey R, et al. Practice parameter: therapies for essential tremor report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2005;64(12):2008-20.
- Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. *Neurology*. 1989;39(12):1587-.
- Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, et al. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. *Canadian Journal of Neurological Sciences*. 2016;43(4):462-71.
- Baizabal-Carvallo JF, Kagnoff MN, Jimenez-Shahed J, Fekete R, Jankovic J. The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. *J Neurol Neurosurg Psychiatry*. 2014;85(5):567-72.
- Mogensen C. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J (Clin Res Ed)*. 1982;285(6343):685-8.
- Brin M, Lyons K, Doucette J, Adler CH, Caviness JN, Comella C, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology*. 2001;56(11):1523-8.
- Mittal SO, Jog M, Lee J, Jabbari B. Novel botulinum toxin injection protocols for parkinson tremor and essential tremor—the yale technique and sensor-based kinematics procedure for safe and effective treatment. *Tremor and Other Hyperkinetic Movements*. 2020;10.
- Samotus O, Lee J, Jog M. Long-term tremor therapy for Parkinson and essential tremor with sensor-guided botulinum toxin type A injections. *PLoS One*. 2017;12(6):e0178670.
- Liao Y-H, Hong C-T, Huang T-W. Botulinum Toxin for Essential Tremor and Hands Tremor in the Neurological Diseases: A Meta-Analysis of Randomized Controlled Trials. *Toxins*. 2022;14(3):203.
- Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Movement Disorders*. 2010;25(5):534-41.
- Kim SD, Yiannikas C, Mahant N, Vucic S, Fung VS. Treatment of proximal upper limb tremor with botulinum toxin therapy. *Movement Disorders*. 2014;29(6):835-8.
- Samotus O, Rahimi F, Lee J, Jog M. Functional Ability Improved in Essential Tremor by IncobotulinumtoxinA Injections Using Kinematically Determined Biomechanical Patterns—A New Future. *PloS one*. 2016;11(4):e0153739.
- Joshi TN, Joshi S. Adverse effects of botulinum neurotoxin A in spasticity management. *International Journal of Nutrition, Pharmacology, Neurological Diseases*. 2011;1(2):126.
- Trosch R, Pullman S. Botulinum toxin A injections for the treatment of hand tremors. *Movement disorders*. 1994;9(6):601-9.
- Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Movement Disorders*. 1996;11(3):250-6.
- Pacchetti C, Mancini F, Bulgheroni M, Zangaglia R, Cristina S, Sandrini G, et al. Botulinum toxin treatment for functional disability induced by essential tremor. *Neurological Sciences*. 2000;21(6):349-53. Disease and Mild Cognitive Impairment Patients. *PLoS One*. 2016;11(7):e0159099-e.